REMARKS

Claims 2-7, 9, and 12-15 remain pending in the present application. Reconsideration of the application in view of the following comments is respectfully requested.

Rejection under 35 U.S.C. § 103

The Examiner maintains the rejection of Claims 2, 5-7, 9, and 14-15 under 35 U.S.C. § 103(a) as being unpatentable over Bianchi et al. (Prenatal Diagnosis, vol. 13, 293-300, 1993) in view of Hume et al. (Early Human Development, vol. 42, no. 2, 1995, pp. 85-95) and Hume et al. (Blood, vol. 87, no. 2, 1996, pp. 762-770). The Examiner rejected Claim 13 under 35 U.S.C. § 103(a) in view of the above references, in further view of Maggio (Immunoenzyme Technique I, CRC Press © 1980, pages 186-187).

Glucose-6-Phosphatase Is Not a Cell Surface Exposed Component

According to the Examiner, Bianchi et al. differs from the present claims solely in failing to teach a method of identifying and isolating embryonic or fetal red blood cells via an adult liver component that is cell surface exposed. In the Office Action, the Examiner stated that "glucose-6-phosphatase is a 'cell surface exposed component' because it can be exposed for visual identification and cell isolation as supported in the references of Hume et al. (1995-page 87-88 Cell Counting/1996-page 763 Cell Counting) and on (sic) the specification (page 10, section 0058)." Also, the Examiner believes that the Specification teaches that glucose-6-phosphatase is an adult liver component meeting the limitations of the claim.

However, scientific evidence demonstrates that glucose-6-phosphatase is not cell-surface exposed. In the attached Chou et al. reference, the third sentence of the abstract states that glucose-6-phosphatase is associated with the endoplasmic reticulum membrane. Figure 2 of Chou et al. illustrates the intracellular localization of glucose-6-phosphatase at the endoplasmic reticulum and not on the cell membrane. Thus, the Chou et al. reference demonstrates that glucose-6-phosphatase is not exposed on the cell surface.

Furthermore, Table 1 of the attached Teasdale and Jackson reference shows that glucose-6-phosphatase has a subcellular localization in the endoplasmic reticulum and contains the endoplasmic reticulum localization motif of VLGQPHKKSL, also known as an endoplasmic reticulum retrieval signal. This bilysine retrieval sequence ensures that glucose-6-phosphatase

cannot move to the plasma membrane. This is clearly stated in the attached Martine et al. reference on page 3546, second column, lines 10-13: "In conclusion, the evidence available suggests that KKXX-containing reporter proteins are restricted to the ER [endoplasmic reticulum] by means of an efficient retrieval mechanism."

The references provide clear evidence that glucose-6-phosphatase is an endoplasmic reticular protein which is present intracellularly and is not cell-surface exposed. Proteins present in the endoplasmic reticulum are transported throughout the cell or extruded through the plasma membrance via the golgi apparatus. Glucose -6-phosphatase is indeed extruded through the membrane. However, its extrusion in the plasma still does not qualify it as a cell-surface exposed component. Extrusion, according to the Oxford English Dictionary, is "The action of pushing out; expulsion by mechanical force; expulsion by violent or rigorous measures from an abode, place, position of privilege, etc." This definition means that glucose-6-phosphatase or the endoplasmic reticulum in which it is contained is extruded externally into the plasma. There is no evidence in the literature to suggest that glucose-6-phosphatase is incorporated into the plasma membrane of erythrocytes.

The Examiner states that Paragraph [0058] of the Specification shows glucose-6-phosphatase to be a cell-surface exposed component. However, Paragraph [0058] clearly and explicitly deals with intracellular components, such as enzymes, which can be detected by virtue of the product formed after the enzyme's substrate enters the cell.

Hume et al. References Do Not Teach a Cell Surface Exposed Component

Also, according to the Examiner, Hume et al. (Early Human Development, vol. 42, no. 2, 1995, pp. 85-95) and Hume et al. (Blood, vol. 87, no. 2, 1996, pp. 762-770) teach that the predominantly hepatic protein (glucose-6-phosphatase) in adults is present in nucleated embryonic and fetal red blood cells and is useful in diagnosis of disorders associated with liver protein expression in the first trimester maternal circulation.

However, careful reading of both Hume et al. references reveals that detection of glucose-6-phosphatase in the references is performed intracellularly and not on intact cells. In absence of any steps to permeabilize cells, the antibodies used by Hume et al. would not detect glucose-6-phosphatase in an intact cell. The examples in both Hume et al. references describe fetal tissue samples that were fixed in 10% formalin for 5 days before being embedded in paraffin wax. The

fixed samples were cut into 3 Tm sections. Figure 1 of both Hume et al. references shows immunohistochemistry of blood cells is 7 Tm in diameter. However, embryonic/fetal red blood cells are larger (megaloblasts or megalocysts). Thus, the 3 Tm sections would have exposed the interior of the cells, allowing the antibodies to bind to intra-cellular glucose-6-phosphatase. There is no evidence that the anti-glucose-6-phosphatase antibodies in Hume et al. would bind to intact cells; indeed, they would not do so.

Accordingly, through use of the literature and analysis of the Specification, it is determined that glucose-6-phosphatase is not a cell-surface exposed component. Therefore, the cited prior art does not teach or suggest all the limitations of the present claims.

Bianchi et al. Teaches Away from Claimed Invention

Furthermore, Bianchi et al. (Prenatal Diagnosis, vol. 13, 293-300, 1993) teaches away from the claimed invention. Thus, it is improper to combine Bianchi with the Hume references.

Bianchi et al. describe a method for detection of fetal nucleated erythrocytes in maternal blood, using gender prediction as a measure of successful fetal cell enrichment. Using anti-CD71 antibodies, Bianchi et al. were 57% successful; using anti-CD36 antibodies they were 88% successful; and using anti-GPA antibodies (either with anti-CD36 or anti-CD71, or alone) they were 100% successful in gender prediction (see Abstract).

To the skilled person, the results of Bianchi et al. are clear: anti-GPA antibodies are particularly useful in fetal cell separation from maternal blood. GPA is taught to be an erythrocyte-specific antigen (see Abstract). Therefore, if the skilled person was motivated to develop further methods for isolating fetal cells from maternal cells, the skilled person would have tested antibodies against other erythrocyte-specific antigens.

Prior to March 1997, the priority date of the present application, antibodies against erythrocyte-specific antigens were used in attempts to enrich for fetal blood cells. Bianchi et al. (1993) is one such example. Erythrocytes were known to express several surface antigens which could be used in methods for fetal cell enrichment (see Table 1 of Alter, 1994). Another example of an erythroid specific antigen is the erythropoietin receptor. Following the teachings of Bianchi et al., the skilled person would have utilized antibodies against other erythrocyte-specific antigens, and certainly not adult liver components as presently claimed.

There is nothing in Bianchi et al. (1993) that would cause the skilled person to consider the two Hume et al. references. Nevertheless, even if the skilled person did combine the teachings of Bianchi et al and Hume et al. references, this would not make the claimed invention, as discussed above.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and comments, it is respectfully submitted that the present application is fully in condition for allowance, and such action is earnestly solicited.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully invited to call the undersigned in order to resolve such issue promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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